2-11-04 Image AE $ 1623

Attorney Docket No. 5576-132 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Maruyama
Serial No. 09/963,738
Filed: September 26, 2001
For: *BASE MATERIAL FOR DRY DIRECT TABLETING COMPRISING LOW SUBSTITUTED HYDROXYPROPYL CELLULOSE*

Confirmation No. 9282
Group Art Unit: 1623
Examiner: E. White

February 10, 2004

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF
(PATENT APPLICATION--37 C.F.R. § 1.192)

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF for the above-identified application, pursuant to the Notice of Appeal filed on December 11, 2003.

2. This application is filed on behalf of
☐ a small entity.

3. Pursuant to 37 C.F.R. § 1.17(c), the fee for filing the Appeal Brief is:
☐ small entity $165.00
☒ other than small entity $330.00

Appeal Brief fee due $330.00

☒ Any additional fee or refund may be charged to Deposit Account 50-0220.

Respectfully submitted,

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Date of Deposit: February 10, 2004

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Susan E. Freedman
Date of Signature: February 10, 2004

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APPELLANT'S BRIEF ON APPEAL UNDER 37 C.F.R. § 1.192

Sir:

This Appeal Brief is filed in triplicate pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed on December 11, 2003 and received by the United States Patent and Trademark Office on December 12, 2003.

REAL PARTY IN INTEREST

The real party in interest is Shin-Etsu Chemical Co., Ltd of Tokyo, Japan, the assignee of the rights to this application by virtue of assignment from the inventor recorded at the United States Patent and Trademark Office on September 26, 2001 on Reel 012203, Frame 0917.

RELATED APPEALS AND INTERFERENCES

Appellants are aware of no appeals or interferences that would be affected by the present appeal.

STATUS OF CLAIMS

Claims 1-21 are pending in the present application as of the filing date of this Appeal Brief. Appellant appeals the final rejection of claims 1-21. As of the filing

date of this Appeal Brief, claims 1-21 remain rejected under 35 U.S.C. § 103(a). A copy of claims 1-21 is attached hereto as **Appendix A** presenting the claims at issue as finally rejected in the Final Office Action dated June 12, 2003 and as entered for purposes of Appeal in the Advisory Action dated September 26, 2003.

STATUS OF AMENDMENTS

An Amendment After Final was filed on September 12, 2003. The Advisory Action dated September 26, 2003 states that the proposed amendment will be entered. Accordingly, all amendments made by Appellant during prosecution are believed to be entered.

SUMMARY OF THE INVENTION

The present invention, as recited in claims 1-21, generally relates to novel dry direct tableting materials comprising low-substituted hydroxypropyl cellulose that can be added for the purpose of imparting disintegration properties or binding properties during the manufacture of preparations in the fields of medicines, foods and the like.

The present invention provides modified low-substituted hydroxypropyl cellulose. The modified low-substituted hydroxypropyl cellulose of the present invention can be added, for example, as a binder and disintegrator in the formation of tablets to serve as a base material for dry direct tableting having desirable properties such as high binding power, good flowability and good disintegrability. *See* Present Application, page 4, lines 15-18.

ISSUES

Whether claims 1-20 are obvious under 35 U.S.C. § 103(a) in view of PCT published application WO 98/53798 to Shimizu and further in view of U.S. Patent No. 3,852,421 to Koyanagi et al.

Whether claim 21 is obvious under 35 U.S.C. § 103(a) in view of PCT published application WO 98/53798 to Shimizu in view of U.S. Patent No. 3,852,421 to Koyanagi et al. and further in view of U.S. Patent No. 6,380,381 to Obara.

GROUPING OF CLAIMS

For the purposes of this Appeal with respect to the outstanding obviousness rejections, the claims may be grouped together as follows:

Group I: Claims 1-20; and

Group II: Claim 21.

The claims of Group I stand or fall together, and the claim within Group II stands or falls together.

ARGUMENT

I. Legal Standard of Obviousness

Appellant notes that a determination under 35 U.S.C. §103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. The Patent Office has the initial burden under §103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations of the present invention. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

In the present case, the Examiner has not established a *prima facie* case of obviousness because the cited references fail to teach or suggest all the claim recitations of the present invention, fail to suggest the modification of the references, to enable the skilled artisan to arrive at the claimed invention, and lastly, fail to provide a reasonable expectation of success.

II. The Rejection

In the Final Office Action dated June 12, 2003 (the Final Action), claims 1-21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over PCT published application WO 98/53798 to Shimizu (Shimizu) and further in view of U.S. Patent No. 3,852,421 to Koyanagi et al. (Koyanagi et al.). Claim 21 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Shimizu in view of Koyanagi et al., and further in view of U.S. Patent No. 6,380,381 to Obara (Obara). The Examiner has withdrawn the rejection under 35 U.S.C. §112, but maintains the rejections under 35 U.S.C. §103 in the Advisory Action dated September 26, 2003 (the Advisory Action).

Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al. and that claim 21 is not obvious in view of Shimizu in view of Koyanagi et al. and further in view of Obara. Accordingly, Appellant respectfully requests reversal of the rejection of claims 1-20 and claim 21 for reasons provided below.

III. Claims 1-20 Are Not Obvious Under 35 U.S.C. § 103(a) In View of WO 98/53798 to Shimizu and Further in View of U.S. Patent No. 3,852,421 to Koyanagi et al.

In the Advisory Action, the Examiner maintains the rejections of claims 1-20 as set forth in the Final Action. More specifically, Appellant previously argued that the claimed invention is indeed patentably distinguished over Shimizu and directed the Examiner's attention to the use of the fluidized bed granulator in Shimizu as shown specifically in Working Example 6 and others. Appellant noted that employing a fluidized bed granulator enables the sugar alcohol to attach only to the **surface** of the low-substituted hydroxypropyl cellulose.

In stark contrast, according to embodiments of the present invention, the low-substituted hydroxypropyl cellulose is **impregnated** with a sugar or sugar alcohol. Upon drying, the sugar or sugar alcohol exists **inside** the low-substituted hydroxypropyl cellulose. As a result, **structurally different** products are provided by the present invention than the product presented by Shimizu. These structurally

different products further provide improved properties that render the products useful for, among other things, dry direct tableting. Thus, in view of the structurally distinct products of the claimed invention, Appellant respectfully submitted that claims 1-20 are not obvious in view of Shimizu.

In the Examiner's response presented in the Advisory Action, the Examiner states that Appellant's argument is not persuasive "since the processes for preparing the low-substituted hydroxypropyl cellulose/sugar alcohol product disclosed in the Shimizu reference are not limited to granulation (see page 14, lines 21-23 of the Shimizu reference)." Advisory Action, page 2.

Referring specifically to page 14, lines 21-23 of Shimizu, Shimizu states that "[t]he blending procedure can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc." Shimizu does not teach or suggest **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol. The mere mention of different methods for carrying out a general blending procedure is not a substitute for the teachings of the present invention of providing, among other things, low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol as recited in claim 1. Moreover, the present application further teaches the following:

> A powder obtained simply by granulating low-substituted hydroxypropyl cellulose with the aid of water and drying the resulting granular material shows an improvement in flowability. However, this powder is reduced to finer particles as a result of shrinkage on drying. Moreover, this powder is reluctant to deformation in response to the force applied during tableting, thus showing a reduction in binding power. However, in the product of the present invention which is obtained by impregnating low-substituted hydroxypropyl cellulose with a sugar or a sugar alcohol and then drying it, the low-substituted hydroxypropyl cellulose is dried after the sugar or sugar alcohol is introduced into its interstices formed as a result of swelling by water. Consequently, it is believed that the shrinkage of the low-substituted hydroxypropyl cellulose on drying is suppressed. Moreover, owing to the presence of the interstitial sugar or sugar alcohol, the low-substituted hydroxypropyl cellulose easily deforms in response to the force applied during tableting and can hence retain its binding power.

Present Application, page 9, line 21 through page 10, line 14.

On page 10, line 15 through page 11, line 11, among other places, the present application provides further details regarding (a) the amount of sugar or sugar alcohol

introduced into the low-substituted hydroxypropyl cellulose and consequences associated therewith, (b) the amount of water used during the process and (c) various options for carrying out impregnation. Thus, in contrast to the Examiner's assertion, Shimizu does not teach or suggest a process or product that provides a dry direct tableting base material comprising low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol.

The missing recitations are not supplied by Koyanagi et al. Koyanagi et al. merely proposes an excipient that comprises hydroxy alkyl cellulose or hydroxy alkyl alkyl cellulose for shaping medicaments into a solid body that can be disintegrated in the human body. *See* Abstract and column 1, lines 9-11. Koyanagi et al. does not teach or suggest a dry direct tableting base material comprising low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol wherein the product resulting therefrom is dried, and wherein said low-substituted hydroxypropyl cellulose has a hydroxypropyl content in the range from 5 to 16% by weight as recited in claim 1.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

IV. Motivation to Modify Shimizu Cannot be Derived From Applicant's Specification

Appellant respectfully submits that any motivation to modify Shimizu is derived from the disclosure in Appellant's specification. However, the Federal Circuit has repeatedly warned that the requisite motivation must come from the cited reference and not Applicant's specification. *See In* re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988); *see also Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988). Moreover, the cited reference must suggest the desirability of the modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1989).

In the instant case, as noted above, Shimizu does not teach or suggest **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol. Instead, Shimizu merely mentions different methods for carrying out a general blending

procedure. Appellant respectfully submits that it is only in view of the present application disclosing **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol, that one of ordinary skill in the art is able to arrive at the present invention. Consequently, it is only through impermissible hindsight that modification of Shimizu would enable one of ordinary skill in the art to arrive at the dry direct tableting base material of the present invention.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

V. Declaration Under 37 C.F.R. § 1.132 of Naosuke Maruyama

Based upon reasons previously made of record, and further in view of the foregoing, Appellant does not believe that a *prima facie* case of obviousness has been established by the Examiner. As a precautionary measure, however, Appellant previously submitted a Declaration Under 37 C.F.R. § 1.132 of Naosuke Maruyama ("Maruyama Declaration"). A copy of which is attached as **Appendix B**.

In general, the Maruyama Declaration presents comparative data illustrating how structural differences affect properties such as flowability index and disintegration time. Results of the comparative data show that the product provided by Shimizu has a lower flowability index as well as a longer disintegration time as compared to the base materials provided in Examples 1 through 4 of the present application. Despite these unexpected results, the Examiner states that the declaration presented by Naosuke Maruyama "is not persuasive since the amount of low-substituted hydroxypropyl cellulose and sugar alcohol recited in Comparative Example 2 of the declaration appear to be substantially different from the amount of material disclosed in the instant claims." Advisory Action, page 2.

As noted during the teleconference with the Examiner on November 14, 2003, 66.7 g of erythritol and 133.3 g of low-substituted hydroxypropyl cellulose in Comparative Example 2 is clearly within the scope of present claims, in particular, claim 9 wherein the sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on the low-substituted hydroxypropyl cellulose. Thus, 50% by weight

erythritol based on the low-substituted hydroxypropyl cellulose was used to make a comparison to other low-substituted hydroxypropyl cellulose products.

Appellant further notes that the present invention satisfies the desirable properties relating to a flowability index of 60 or more, a binding power of 150N or more, and a disintegration time of 6 minutes or less as shown through the comparative data. Specifically comparing Comparative Example 2 in the Maruyama Declaration with Examples 1-4 of the present application, it can be observed that the flowability index is 61 to 67 for Examples 1-4, while the flowability index is 58 for Comparative Example 2. In contrast to the assertions of the Examiner, a flowability index of 58 is not within error of a flowability index of 61. It should be noted that a powder having a flowability index of 58 is highly likely to cause bridging in a hopper during tableting, however, a powder having a flowability index of 60 or more is not likely to cause bridging in a hopper during tableting. The binding power is 170-350N for Examples 1-4 and 188N for Comparative Example 2. For Examples 1-4, the disintegrability time is 2.3-5.4 minutes for Examples 1-4 and 8 minutes for Comparative Example 2. Clearly, the present invention provides compositions that excel in the total coordination of all three properties– flowability index, binding power and disintegrability.

In view of the arguments set forth, along with comparative data presented in the Declaration of Naosuke Maruyama, Appellant respectfully submits that one of ordinary skill in the art to which the present invention pertains would not rely upon the Shimizu reference proposing a mere combination of components yielding a solid pharmaceutical preparation, in order to arrive at the structurally distinct base materials of the present invention.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

VI. Claim 21 Is Not Obvious Under 35 U.S.C. § 103 (a) In View of The Combination of Shimizu, Koyanagi et al., and/or Obara

Appellant respectfully submits that claim 21 is not obvious in view of the combination of Shimizu, Koyanagi et al., and/or Obara. For reasons set forth above,

Shimizu, alone or in combination with Koyanagi et al., does not render the present invention obvious. The missing recitations are not supplied by Obara which merely proposes a low-substituted hydroxypropyl cellulose that is clearly distinct from the dry direct tableting base materials of the present invention. In fact, the Examiner states that "[t]he Koyanagi et al. patent is only cited to show that tableting hydroxypropyl cellulose by dry and direct compression is well known in the art. The Obara patent is only cited to show that use of low-substituted hydroxypropyl cellulose in fibrous form to prepare tablets is known in the art." Advisory Action, page 2. Thus, conventional tableting formulation, as proposed by both Shimizu and Koyanagi et al., does not provide the improved product as recited in claim 1 and claims dependent therefrom, and Obara does not supply the missing recitations or motivation to arrive at the claimed invention. Consequently, Appellant respectfully submits that for the reasons discussed above, the dry direct tableting base materials, as recited in claim 21, are patentably distinct from the product provided by Shimizu alone or in combination with Koyanagi et al. and/or Obara.

Accordingly, Appellant respectfully submits that claim 21 is not obvious in view of Shimizu alone or in combination with Koyanagi et al. and/or Obara, and respectfully requests reversal of the rejection of claim 21.

In sum, the present invention excels in a total coordination of flowability index, binding power and disintegrability. As a tablet exhibits a higher degree of hardness, i.e., binding power, the disintegration time generally tends to increase. As a tablet exhibits higher powder flow, i.e., higher flowability index, the binding power tends to decrease. Thus, these properties are in conflict. The present invention, however, excels in total coordination of flowability index, binding power and disintegrability.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al. Additionally, Appellant respectfully submits that claim 21 is not obvious in view of the combination of Shimizu, Koyanagi et al., and/or Obara.

CONCLUSION

In light of the entire record and the above discussion, Appellant respectfully submits that claims 1-20 and claim 21 are patentable over the cited references. Accordingly, Appellant respectfully requests reversal of the pending rejection of claims 1-20 and claim 21, and that this case be passed to issuance.

Respectfully submitted,

Shawna Cannon Lemon
Registration No. 53,888

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Susan E. Freedman
Date of Signature: February 10, 2004

TABLE OF AUTHORITIES

CASES

STATUTES

OTHER AUTHORITIES

APPENDIX A

What is Claimed is:

1. (Previously Presented) A dry direct tableting base material comprising low-substituted hydroxypropyl cellulose impregnated with a sugar or a sugar alcohol wherein the product resulting therefrom is dried, and wherein said low-substituted hydroxypropyl cellulose has a hydroxypropyl content in the range from 5 to 16 % by weight.

2. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said low-substituted hydroxypropyl cellulose has a degree of compaction of 35% or greater.

3. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said base material has a flowability index of 60 or greater.

4. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said base material has a flowability index of 60 or greater.

5. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

6. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

7. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

8. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

9. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

10. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

11. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

12. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

13. (Previously Presented) The dry direct tableting base material as claimed in claim 5 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

14. (Previously Presented) The dry direct tableting base material as claimed in claim 6 wherein said sugar or sugar alcohol is present in an amount of 30 or 100% by weight based on said low-substituted hydroxypropyl cellulose.

15. (Previously Presented) The dry direct tableting base material as claimed in claim 7 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

16. (Previously Presented) The dry direct tableting base material as claimed in claim 8 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

17. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

18. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

19. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

20. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

21. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said low-substituted hydroxypropyl cellulose is in fibrous form.

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Maruyama Art Unit: 1623

Serial No. : 09/963,738 Examiner: Everett White

Filing Date: September 26, 2001

For: Base Material for Dry Direct Tableting Comprising Low-substituted Hydroxypropyl Cellulose

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO RULE 132

I, Naosuke Maruyama, hereby sincerely and solemnly declares that

1. I completed a bachelor course at Nagoya City University in March, 1988, being specialized in biochemical of pharmaceutics. Since April , 1988, I have been employed by Sin-Etsu Chemical Co., Ltd., assignee of the above-identified application where I have been engaged in research focusing mainly on Pharmaceutical Technology Solid Dosage Forms. The publications include "Dry coating using enteric polymeric powder ", Journal of Powder Technology Japan , 35(1998) 447-450 ; "Dry coating: an innovative enteric coating method using a cellulose derivative" , European Journal of Pharmaceutics and Biopharmaceutics 47 (1999) 51-59. I am an inventor of the above-identified application and I am familiar with the subject matter disclosed in the application as well as the disclosures in the references cited against the claims.

2. In order to further prove the improved properties of the solid preparation of the present invention, the following preparation was produced.

<Comparative Example 2>

A fluidized bed granulator (Maltiplex MP-01, manufactured by Powrex Corp. in Japan) was charged with 66.7 g of erythritol and 133.3 g of low-substituted hydroxypropylcellulose (LH-11, manufactured by Shin-Etsu Chemical Co., Ltd. in Japan) containing 0.25 mole of hydroxypropoxyl substituent group. The granulation was carried out at an air flow of 60 m^3/hr and at temperatures of 60℃ for inhalation of air and 35℃ for discharge of air, while spraying 60g of distilled water at the rate of 10 g/min. The granules were dried in a hot-air oven at 80℃. The dried granules which had passed through 80-mesh screen with opening of 177 μm were collected.

The obtained granules were evaluated in the manner described in the specification. The result was as follows.

flowability index: 58
binding power: 188 N
disintegration time: 8.0 min.

3. According to Comparative Example 2, lower flowability index and longer disintegration time were observed in comparison with those of Examples 1 to 4 in Table 1 of the specification. Thus, it is evident that the base material of the present invention gives rises to the unexpected result.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Dated: August, 18 2003

Naosuke Maruyama

Attorney Docket No. 5576-132 PATENT

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Sir:

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The present invention provides modified low-substituted hydroxypropyl cellulose. The modified low-substituted hydroxypropyl cellulose of the present invention can be added, for example, as a binder and disintegrator in the formation of tablets to serve as a base material for dry direct tableting having desirable properties such as high binding power, good flowability and good disintegrability. *See* Present Application, page 4, lines 15-18.

ISSUES

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ARGUMENT

I. Legal Standard of Obviousness

Appellant notes that a determination under 35 U.S.C. §103 that an invention would have been obvious to someone of ordinary skill in the art is a conclusion of law based on fact. *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1593, 1 U.S.P.Q.2d 1593 (Fed. Cir. 1987), *cert. denied*, 107 S.Ct. 2187. The Patent Office has the initial burden under §103 to establish a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988).

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim recitations of the present invention. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

In the present case, the Examiner has not established a *prima facie* case of obviousness because the cited references fail to teach or suggest all the claim recitations of the present invention, fail to suggest the modification of the references, to enable the skilled artisan to arrive at the claimed invention, and lastly, fail to provide a reasonable expectation of success.

II. The Rejection

In the Final Office Action dated June 12, 2003 (the Final Action), claims 1-21 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over PCT published application WO 98/53798 to Shimizu (Shimizu) and further in view of U.S. Patent No. 3,852,421 to Koyanagi et al. (Koyanagi et al.). Claim 21 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Shimizu in view of Koyanagi et al., and further in view of U.S. Patent No. 6,380,381 to Obara (Obara). The Examiner has withdrawn the rejection under 35 U.S.C. §112, but maintains the rejections under 35 U.S.C. §103 in the Advisory Action dated September 26, 2003 (the Advisory Action).

Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al. and that claim 21 is not obvious in view of Shimizu in view of Koyanagi et al. and further in view of Obara. Accordingly, Appellant respectfully requests reversal of the rejection of claims 1-20 and claim 21 for reasons provided below.

III. Claims 1-20 Are Not Obvious Under 35 U.S.C. § 103(a) In View of WO 98/53798 to Shimizu and Further in View of U.S. Patent No. 3,852,421 to Koyanagi et al.

In the Advisory Action, the Examiner maintains the rejections of claims 1-20 as set forth in the Final Action. More specifically, Appellant previously argued that the claimed invention is indeed patentably distinguished over Shimizu and directed the Examiner's attention to the use of the fluidized bed granulator in Shimizu as shown specifically in Working Example 6 and others. Appellant noted that employing a fluidized bed granulator enables the sugar alcohol to attach only to the **surface** of the low-substituted hydroxypropyl cellulose.

In stark contrast, according to embodiments of the present invention, the low-substituted hydroxypropyl cellulose is **impregnated** with a sugar or sugar alcohol. Upon drying, the sugar or sugar alcohol exists **inside** the low-substituted hydroxypropyl cellulose. As a result, **structurally different** products are provided by the present invention than the product presented by Shimizu. These structurally

different products further provide improved properties that render the products useful for, among other things, dry direct tableting. Thus, in view of the structurally distinct products of the claimed invention, Appellant respectfully submitted that claims 1-20 are not obvious in view of Shimizu.

In the Examiner's response presented in the Advisory Action, the Examiner states that Appellant's argument is not persuasive "since the processes for preparing the low-substituted hydroxypropyl cellulose/sugar alcohol product disclosed in the Shimizu reference are not limited to granulation (see page 14, lines 21-23 of the Shimizu reference)." Advisory Action, page 2.

Referring specifically to page 14, lines 21-23 of Shimizu, Shimizu states that "[t]he blending procedure can be carried out by any of the conventional blending techniques such as admixing, kneading, granulating, etc." Shimizu does not teach or suggest **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol. The mere mention of different methods for carrying out a general blending procedure is not a substitute for the teachings of the present invention of providing, among other things, low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol as recited in claim 1. Moreover, the present application further teaches the following:

> A powder obtained simply by granulating low-substituted hydroxypropyl cellulose with the aid of water and drying the resulting granular material shows an improvement in flowability. However, this powder is reduced to finer particles as a result of shrinkage on drying. Moreover, this powder is reluctant to deformation in response to the force applied during tableting, thus showing a reduction in binding power. However, in the product of the present invention which is obtained by impregnating low-substituted hydroxypropyl cellulose with a sugar or a sugar alcohol and then drying it, the low-substituted hydroxypropyl cellulose is dried after the sugar or sugar alcohol is introduced into its interstices formed as a result of swelling by water. Consequently, it is believed that the shrinkage of the low-substituted hydroxypropyl cellulose on drying is suppressed. Moreover, owing to the presence of the interstitial sugar or sugar alcohol, the low-substituted hydroxypropyl cellulose easily deforms in response to the force applied during tableting and can hence retain its binding power.

Present Application, page 9, line 21 through page 10, line 14.

On page 10, line 15 through page 11, line 11, among other places, the present application provides further details regarding (a) the amount of sugar or sugar alcohol

introduced into the low-substituted hydroxypropyl cellulose and consequences associated therewith, (b) the amount of water used during the process and (c) various options for carrying out impregnation. Thus, in contrast to the Examiner's assertion, Shimizu does not teach or suggest a process or product that provides a dry direct tableting base material comprising low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol.

The missing recitations are not supplied by Koyanagi et al. Koyanagi et al. merely proposes an excipient that comprises hydroxy alkyl cellulose or hydroxy alkyl alkyl cellulose for shaping medicaments into a solid body that can be disintegrated in the human body. *See* Abstract and column 1, lines 9-11. Koyanagi et al. does not teach or suggest a dry direct tableting base material comprising low-substituted hydroxypropyl cellulose **impregnated** with a sugar or a sugar alcohol wherein the product resulting therefrom is dried, and wherein said low-substituted hydroxypropyl cellulose has a hydroxypropyl content in the range from 5 to 16% by weight as recited in claim 1.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

IV. Motivation to Modify Shimizu Cannot be Derived From Applicant's Specification

Appellant respectfully submits that any motivation to modify Shimizu is derived from the disclosure in Appellant's specification. However, the Federal Circuit has repeatedly warned that the requisite motivation must come from the cited reference and not Applicant's specification. *See In* re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988); *see also Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907 (Fed. Cir. 1988). Moreover, the cited reference must suggest the desirability of the modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1989).

In the instant case, as noted above, Shimizu does not teach or suggest **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol. Instead, Shimizu merely mentions different methods for carrying out a general blending

procedure. Appellant respectfully submits that it is only in view of the present application disclosing **impregnating** low-substituted hydroxypropyl cellulose with a sugar alcohol, that one of ordinary skill in the art is able to arrive at the present invention. Consequently, it is only through impermissible hindsight that modification of Shimizu would enable one of ordinary skill in the art to arrive at the dry direct tableting base material of the present invention.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

V. Declaration Under 37 C.F.R. § 1.132 of Naosuke Maruyama

Based upon reasons previously made of record, and further in view of the foregoing, Appellant does not believe that a *prima facie* case of obviousness has been established by the Examiner. As a precautionary measure, however, Appellant previously submitted a Declaration Under 37 C.F.R. § 1.132 of Naosuke Maruyama ("Maruyama Declaration"). A copy of which is attached as **Appendix B**.

In general, the Maruyama Declaration presents comparative data illustrating how structural differences affect properties such as flowability index and disintegration time. Results of the comparative data show that the product provided by Shimizu has a lower flowability index as well as a longer disintegration time as compared to the base materials provided in Examples 1 through 4 of the present application. Despite these unexpected results, the Examiner states that the declaration presented by Naosuke Maruyama "is not persuasive since the amount of low-substituted hydroxypropyl cellulose and sugar alcohol recited in Comparative Example 2 of the declaration appear to be substantially different from the amount of material disclosed in the instant claims." Advisory Action, page 2.

As noted during the teleconference with the Examiner on November 14, 2003, 66.7 g of erythritol and 133.3 g of low-substituted hydroxypropyl cellulose in Comparative Example 2 is clearly within the scope of present claims, in particular, claim 9 wherein the sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on the low-substituted hydroxypropyl cellulose. Thus, 50% by weight

erythritol based on the low-substituted hydroxypropyl cellulose was used to make a comparison to other low-substituted hydroxypropyl cellulose products.

Appellant further notes that the present invention satisfies the desirable properties relating to a flowability index of 60 or more, a binding power of 150N or more, and a disintegration time of 6 minutes or less as shown through the comparative data. Specifically comparing Comparative Example 2 in the Maruyama Declaration with Examples 1-4 of the present application, it can be observed that the flowability index is 61 to 67 for Examples 1-4, while the flowability index is 58 for Comparative Example 2. In contrast to the assertions of the Examiner, a flowability index of 58 is not within error of a flowability index of 61. It should be noted that a powder having a flowability index of 58 is highly likely to cause bridging in a hopper during tableting, however, a powder having a flowability index of 60 or more is not likely to cause bridging in a hopper during tableting. The binding power is 170-350N for Examples 1-4 and 188N for Comparative Example 2. For Examples 1-4, the disintegrability time is 2.3-5.4 minutes for Examples 1-4 and 8 minutes for Comparative Example 2. Clearly, the present invention provides compositions that excel in the total coordination of all three properties– flowability index, binding power and disintegrability.

In view of the arguments set forth, along with comparative data presented in the Declaration of Naosuke Maruyama, Appellant respectfully submits that one of ordinary skill in the art to which the present invention pertains would not rely upon the Shimizu reference proposing a mere combination of components yielding a solid pharmaceutical preparation, in order to arrive at the structurally distinct base materials of the present invention.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al., and respectfully requests reversal of the rejection of claims 1-20.

VI. Claim 21 Is Not Obvious Under 35 U.S.C. § 103 (a) In View of The Combination of Shimizu, Koyanagi et al., and/or Obara

Appellant respectfully submits that claim 21 is not obvious in view of the combination of Shimizu, Koyanagi et al., and/or Obara. For reasons set forth above,

Shimizu, alone or in combination with Koyanagi et al., does not render the present invention obvious. The missing recitations are not supplied by Obara which merely proposes a low-substituted hydroxypropyl cellulose that is clearly distinct from the dry direct tableting base materials of the present invention. In fact, the Examiner states that "[t]he Koyanagi et al. patent is only cited to show that tableting hydroxypropyl cellulose by dry and direct compression is well known in the art. The Obara patent is only cited to show that use of low-substituted hydroxypropyl cellulose in fibrous form to prepare tablets is known in the art." Advisory Action, page 2. Thus, conventional tableting formulation, as proposed by both Shimizu and Koyanagi et al., does not provide the improved product as recited in claim 1 and claims dependent therefrom, and Obara does not supply the missing recitations or motivation to arrive at the claimed invention. Consequently, Appellant respectfully submits that for the reasons discussed above, the dry direct tableting base materials, as recited in claim 21, are patentably distinct from the product provided by Shimizu alone or in combination with Koyanagi et al. and/or Obara.

Accordingly, Appellant respectfully submits that claim 21 is not obvious in view of Shimizu alone or in combination with Koyanagi et al. and/or Obara, and respectfully requests reversal of the rejection of claim 21.

In sum, the present invention excels in a total coordination of flowability index, binding power and disintegrability. As a tablet exhibits a higher degree of hardness, i.e., binding power, the disintegration time generally tends to increase. As a tablet exhibits higher powder flow, i.e., higher flowability index, the binding power tends to decrease. Thus, these properties are in conflict. The present invention, however, excels in total coordination of flowability index, binding power and disintegrability.

Accordingly, Appellant respectfully submits that claims 1-20 are not obvious in view of Shimizu and further in view of Koyanagi et al. Additionally, Appellant respectfully submits that claim 21 is not obvious in view of the combination of Shimizu, Koyanagi et al., and/or Obara.

CONCLUSION

In light of the entire record and the above discussion, Appellant respectfully submits that claims 1-20 and claim 21 are patentable over the cited references. Accordingly, Appellant respectfully requests reversal of the pending rejection of claims 1-20 and claim 21, and that this case be passed to issuance.

Respectfully submitted,

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Susan E. Freedman
Date of Signature: February 10, 2004

TABLE OF AUTHORITIES

CASES

STATUTES

OTHER AUTHORITIES

APPENDIX A

What is Claimed is:

1. (Previously Presented) A dry direct tableting base material comprising low-substituted hydroxypropyl cellulose impregnated with a sugar or a sugar alcohol wherein the product resulting therefrom is dried, and wherein said low-substituted hydroxypropyl cellulose has a hydroxypropyl content in the range from 5 to 16 % by weight.

2. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said low-substituted hydroxypropyl cellulose has a degree of compaction of 35% or greater.

3. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said base material has a flowability index of 60 or greater.

4. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said base material has a flowability index of 60 or greater.

5. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

6. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

7. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

8. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol and sorbitol.

9. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

10. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

11. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

12. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

13. (Previously Presented) The dry direct tableting base material as claimed in claim 5 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

14. (Previously Presented) The dry direct tableting base material as claimed in claim 6 wherein said sugar or sugar alcohol is present in an amount of 30 or 100% by weight based on said low-substituted hydroxypropyl cellulose.

15. (Previously Presented) The dry direct tableting base material as claimed in claim 7 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

16. (Previously Presented) The dry direct tableting base material as claimed in claim 8 wherein said sugar or sugar alcohol is present in an amount of 30 to 100% by weight based on said low-substituted hydroxypropyl cellulose.

17. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

18. (Previously Presented) The dry direct tableting base material as claimed in claim 2 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

19. (Previously Presented) The dry direct tableting base material as claimed in claim 3 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

20. (Previously Presented) The dry direct tableting base material as claimed in claim 4 wherein said sugar or sugar alcohol is one or more compounds selected from the group consisting of erythritol, mannitol, sorbitol, lactose, and sucrose.

21. (Previously Presented) The dry direct tableting base material as claimed in claim 1 wherein said low-substituted hydroxypropyl cellulose is in fibrous form.

APPENDIX B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Maruyama Art Unit: 1623

Serial No. : 09/963,738 Examiner: Everett White

Filing Date: September 26, 2001

For: Base Material for Dry Direct Tableting Comprising Low-substituted Hydroxypropyl Cellulose

Assistant Commissioner for Patents
Washington, D.C. 20231

DECLARATION PURSUANT TO RULE 132

I, Naosuke Maruyama, hereby sincerely and solemnly declares that

1. I completed a bachelor course at Nagoya City University in March, 1988, being specialized in biochemical of pharmaceutics. Since April , 1988, I have been employed by Sin-Etsu Chemical Co., Ltd., assignee of the above-identified application where I have been engaged in research focusing mainly on Pharmaceutical Technology Solid Dosage Forms. The publications include "Dry coating using enteric polymeric powder ", Journal of Powder Technology Japan , 35(1998) 447-450 ; "Dry coating: an innovative enteric coating method using a cellulose derivative" , European Journal of Pharmaceutics and Biopharmaceutics 47 (1999) 51-59. I am an inventor of the above-identified application and I am familiar with the subject matter disclosed in the application as well as the disclosures in the references cited against the claims.

2. In order to further prove the improved properties of the solid preparation of the present invention, the following preparation was produced.

<Comparative Example 2>

A fluidized bed granulator (Maltiplex MP-01, manufactured by Powrex Corp. in Japan) was charged with 66.7 g of erythritol and 133.3 g of low-substituted hydroxypropylcellulose (LH-11, manufactured by Shin-Etsu Chemical Co., Ltd. in Japan) containing 0.25 mole of hydroxypropoxyl substituent group. The granulation was carried out at an air flow of 60 m^3/hr and at temperatures of 60℃ for inhalation of air and 35℃ for discharge of air, while spraying 60g of distilled water at the rate of 10 g/min. The granules were dried in a hot-air oven at 80℃. The dried granules which had passed through 80-mesh screen with opening of 177 μm were collected.

The obtained granules were evaluated in the manner described in the specification. The result was as follows.

flowability index: 58
binding power: 188 N
disintegration time: 8.0 min.

3. According to Comparative Example 2, lower flowability index and longer disintegration time were observed in comparison with those of Examples 1 to 4 in Table 1 of the specification. Thus, it is evident that the base material of the present invention gives rises to the unexpected result.

4. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Dated: August, 18 2003

Naosuke Maruyama